1. INTRODUCTION

1.1. BACKGROUND

1,3-Butadiene (CH_2=CH-CH=CH_2, CAS No. 106-99-0) is a colorless gas produced by three different processes: (1) oxidative dehydrogenation of n-butene (the Oxo-D or O-X-D process), (2) catalytic dehydrogenation of n-butane and n-butene (the Houdry process), and (3) recovery from the C_4 coproduct (by-product) stream from the steam cracking process used to manufacture ethylene (the ethylene coproduct process). This noncorrosive gas has a boiling point of −4.4°C and a vapor pressure of 1,900 mm/Hg at 20°C (Kirshenbaum, 1978). 1,3-Butadiene is highly volatile and has a low solubility in water; thus environmental release results primarily in atmospheric contamination. Atmospheric destruction of 1,3-butadiene occurs primarily by photoinitiated reactions. A significant amount of destruction also occurs by the gas phase reaction with ozone and reaction with nitrate radicals at nighttime, particularly in urban areas (U.S. DHHS, 1992). The major photooxidation products of 1,3-butadiene are acrolein and formaldehyde (Maldotti et al., 1980).

Approximately 12 billion pounds of 1,3-butadiene are produced annually worldwide and 3 billion pounds in the United States (Morrow, 1990; USITC, 1990). It is used as an intermediate in the production of polymers, elastomers, and other chemicals. The major uses of 1,3-butadiene are in the manufacture of styrene-butadiene rubber (SBR) (synthetic rubber) and of thermoplastic resins. Elastomers of butadiene are used in the manufacture of tires, footwear, sponges, hoses and piping, luggage, packaging, and a variety of other molded products. In addition, 1,3-butadiene is used as an intermediate to produce a variety of industrial chemicals, including the fungicides captan and captfol. The primary way the 1,3-butadiene is released in the environment is via emissions from gasoline- and diesel-powered vehicles and equipment. Minor releases occur in production processes, tobacco smoke, gasoline vapors, and vapors from the burning of plastics as well as rubber (Miller, 1978).

1.2. SUMMARY OF PAST CARCINOGEN RISK ASSESSMENTS OF 1,3-BUTADIENE

The purpose of this section is to review past carcinogen risk assessments of 1,3-butadiene. It should be noted that the Toxicological Profile for 1,3-butadiene (ATSDR, 1992), profile of 1,3-butadiene to set the threshhold limit value (TLV) (ACGIH, 1994), and 1,3-Butadiene OEL Criteria Document by the European Center for Ecotoxicology and Toxicology of Chemicals (1997) are not reviewed here as they are not risk assessments.

1.2.1. Summary of EPA's Carcinogen Assessment (U.S. EPA, 1985)

Pertinent studies reported before 1986 were reviewed in Mutagenicity and Carcinogenicity Assessment of 1,3-Butadiene (U.S. EPA, 1985). This document was peer reviewed by experts in the field, as well as in public sessions of the Environmental Health Committee of EPA's Science Advisory Board. The studies presented in the 1985 document will not be reviewed in the present document but are briefly summarized below.

EPA reviewed six epidemiological studies, which included four retrospective cohort mortality studies, one nested case-control study, and an industrial hygiene and hematologic cross-sectional survey. The first cohort study involved 6,678 hourly workers in a rubber tire manufacturing plant in Akron, Ohio (McMichael et al., 1974). The standard mortality ratios (SMRs) were calculated using the 1968 U.S. male population as the reference. Cause-specific mortality was evaluated for 16 different occupational title groups (work areas) within the plant. This study was followed up by a nested case-control study involving 455 of the 1,983 deaths recorded between 1968 and 1973 (McMichael et al., 1976). The second cohort study was conducted in 8,938 male workers in a rubber plant also located in Akron, Ohio (Andjelkovich et al., 1976, 1977). The 1976 study used the U.S. male population as the reference for calculating the SMRs, whereas the entire cohort was used to calculate the SMRs for 28 different work areas for the 1977 study. The third cohort study included 2,756 workers at two styrene-butadiene rubber facilities in eastern Texas (Meinhardt et al., 1982). The sex, age, race, and calendar time cause-specific rates of the U.S. population were used to calculate the SMRs. The last and most comprehensive study was conducted in 13,920 workers at one Canadian and seven U.S. styrene-butadiene rubber plants (Matanoski et al., 1982). The SMRs for black and white workers were calculated separately. The cross-sectional survey was conducted on workers in the same styrene-butadiene rubber plant studied by McMichael et al. (Checkoway and Williams, 1982). Blood samples were obtained to evaluate hematology parameters. The survey was not designed to evaluate mortality experience and did not contribute to cancer risk evaluation of 1,3-butadiene.

Of the five epidemiologic studies that evaluated cause-specific mortality, three cohort studies demonstrated statistically significant excess mortality due to cancers of the lymphatic and hematopoietic tissues (Andjelkovich et al., 1976; McMichael et al., 1976; Meinhardt et al., 1982). The fourth cohort study by Matanoski et al. (1982) also showed increased leukemia, but failed to achieve statistical significance. Lastly, the nested case-control study by McMichael et al. (1976) showed statistically significant increased standardized risk ratios for cancers of the lymphatic and hematopoietic tissues among workers with exposures of 5 years or more in one area of the plant (synthetic rubber plant area), as compared with either all the other workers or the matched controls. Statistically significant excess cancer mortality was also observed for gastrointestinal

tract, respiratory tract, central nervous system, prostate, testicles, and urinary bladder in one or more studies. However, these excesses were not observed consistently across all the studies.

Although excess mortality due to cancers of the lymphatic and hematopoietic tissues was observed consistently in all the evaluated studies, the methodologic limitations, such as too few deaths from specific cancers to evaluate the causal association; exclusion of large portions of the population due to lack of records; lack of adjustment for smoking; confounding by other exposures such as benzene or styrene; and excess cancer mortality at other sites prompted EPA to conclude that the evidence was inadequate for determining a causal association between exposure to 1,3-butadiene and cancer in humans.

Two long-term animal studies presented strong evidence for the induction of cancers at multiple anatomical sites in both rats (HLE, 1981) and mice (NTP, 1984). Sprague-Dawley rats were exposed by inhalation to 1,3-butadiene at concentrations of 1,000 or 8,000 ppm 6 h/day, 5 d/week for 111 weeks and 105 weeks for males and females, respectively. Statistically significant increased incidences in the following neoplasms were observed at one or both concentrations: mammary gland tumors, thyroid follicular adenomas/carcinomas, and Zymbal gland carcinomas in female rats and Leydig cell adenomas/carcinomas, pancreatic exocrine adenomas, and Zymbal gland tumors in male rats. In addition, gliomas occurred in four high-dose male rats. Nonneoplastic effects due to long-term exposure of rats to 1,3-butadiene included clinical signs of toxicity, an increase in liver weight in both sexes, marked to severe nephropathy in 27% of the high-dose male rats compared with 9% or 10% of the controls, and alveolar metaplasia in male rats.

Among B6C3F_1 mice exposed by inhalation to 1,3-butadiene at 625 or 1,250 ppm for 6 h/day, 5 d/week, neoplasms also developed at multiple anatomical sites; this study was terminated at week 60 to 61 because of high mortality in the treated groups, primarily due to neoplasms. There was an overall increase in the number of animals with primary neoplasms and animals with multiple neoplasms. Neoplasms showing statistically significant increased incidences among both male and female mice were as follows: malignant lymphomas, alveolar/bronchiolar adenomas/carcinomas, hemangiosarcomas of the heart, and forestomach papillomas/carcinomas. In addition, mammary gland acinar cell carcinomas, ovarian granulosa cell carcinomas, and hepatocellular adenomas/carcinomas occurred in female mice. Nonneoplastic effects observed were testicular atrophy, chronic inflammation, fibrosis, cartilaginous metaplasia, osseous metaplasia, and atrophy of the sensory epithelium of the nasal cavity in male mice. Ovarian atrophy was observed in female mice. Some discrepancies were noted for this study, but they were not considered to pose a significant impact on the overall interpretation of the study.

EPA also reviewed data from metabolism and mutagenicity studies, concluding that inhaled 1,3-butadiene is metabolized to mutagenic epoxide intermediates.

In addition, EPA reviewed the carcinogenicity of related compounds (4-vinyl-1-cyclohexene, epoxybutene, *dl*-1,2:3,4-diepoxybutane, and *meso*-1,2:3,4-diepoxybutane). 4-Vinyl-1-cyclohexene is carcinogenic in female mice (oral/gavage), based on increased incidences of ovarian and adrenal gland neoplasms. Equivocal evidence was noted for malignant lymphomas and alveolar/bronchiolar adenomas in male mice and clitoral gland neoplasms in female rats (NTP, 1986). Skin painting of mice with *meso*-1,2:3,4-diepoxybutane induced papillomas and squamous cell carcinomas (Van Duuren et al., 1963), and subcutaneous injection with *dl*-1,2:3,4-diepoxybutane caused fibrosarcomas in mice and rats (Van Duuren et al., 1966).

Based on the studies in mice and rats, EPA concluded that there was sufficient evidence for carcinogenicity of 1,3-butadiene in animals. EPA also concluded that evidence from metabolism, mutagenicity, and carcinogenicity studies suggests that 1,3-butadiene presents a genetic risk to humans.

Two developmental toxicity studies were reviewed. One study (HLE, 1981) was conducted using pregnant female Sprague-Dawley rats exposed to 200, 1,000, and 8,000 ppm 6 h/day on gestation days 6-15. Developmental effects included slightly decreased fetal weight and mean crown-rump length and increased skeletal variations and malformations. The other study (Carpenter et al., 1944) was inadequately reported.

EPA presented the following conclusion regarding the qualitative evaluation of the data for 1,3-butadiene: "On the basis of sufficient evidence from studies in two species of rodents, and inadequate epidemiologic data, 1,3-butadiene can be classified as a probable human carcinogen, Group B2." Using the classification scheme of the International Agency for Research on Cancer (IARC), 1,3-butadiene would also be classified as a "probable" human carcinogen, Group 2B.

The linearized multistage model was used to calculate the maximum likelihood estimate for the incremental risk for 1,3-butadiene based upon the National Toxicology Program mouse data (NTP, 1984), the HLE (1981) rat data, and internal dosimetry derived from data on mice and rats exposed to varying concentrations of 1,3-butadiene for 6 h. The upper-limit unit risk of $6.4 \times 10^{-1}(\text{ppm})^{-1}$ was a geometric mean of the values calculated for male and female mice separately. The unit risk extrapolated to humans was $2.5 \times 10^{-2}(\text{ppm})^{-1}$. This value was used to predict human responses in the epidemiologic studies, which were then compared with the actual responses. According to EPA, ". . . The comparisons were hampered by a scarcity of information in the epidemiologic data concerning actual exposures, age distribution, and work histories. In addition, because there was no consistent cancer response across all of the studies, the most predominant response, cancer of the lymphatic and hematopoietic tissues, was chosen as being the target for 1,3-butadiene. Based on the comparisons between the predicted and observed human response, the extrapolated value from the mouse data was consistent with human response, but in view of all the uncertainties and apparent inconsistencies in the epidemiologic data, a fairly wide

range of potency estimates and exposure scenarios would also be satisfactory. . . ." (U.S. EPA, 1985).

1.2.2. Summary of IARC's Evaluation of 1,3-Butadiene (IARC, 1986, 1992)

IARC reported the first evaluation of 1,3-butadiene as a separate chemical in 1986 (IARC, 1986). In an earlier report (IARC, 1982), 1,3-butadiene was evaluated as a chemical used in the rubber industry. IARC's 1986 evaluation of the animal data consisted of the NTP (1984) study using male and female B6C3F$_1$ mice exposed to 625 or 1,250 ppm 1,3-butadiene for 60 or 61 weeks and an abstract description of the HLE (1981) study in rats exposed to 1,000 or 8,000 ppm (Owen et al., 1985). The human data consisted only of a cohort study described by Meinhardt et al. (1982) and a brief mention of the following studies of workers in the rubber industry that were included in IARC's evaluation of the rubber industry: Andjelkovich et al., 1976, 1977; McMichael et al., 1976; and Monson and Nakano, 1976. The supporting evidence considered by IARC consisted of absorption, distribution, metabolism, and excretion (ADME) data. The genotoxicity data showed that 1,3-butadiene was mutagenic in *S. typhimurium* with metabolic activation, and the metabolites (1,2-epoxybutene and 1,2:3,4-diepoxybutane) were mutagenic in *S. typhimurium* without metabolic activation. IARC also evaluated data on acute, reproductive, and developmental toxicity of 1,3-butadiene. IARC (1986) concluded that the supporting evidence for genetic activity was "inadequate," the evidence for carcinogenicity in experimental animals was "sufficient," and the evidence for carcinogenicity in humans was "inadequate" (Group 2B).

IARC reevaluated the data on 1,3-butadiene and reported the results in 1992. Additional animal and human studies were available for evaluation. In addition to the first NTP (1984) study in mice, IARC (1992) evaluated a more recent NTP study reported by Melnick et al. (1990a). In this study, male and female B6C3F$_1$ mice exposed by inhalation to 1,3-butadiene at concentrations of 6.25 to 625 ppm for 2 years developed neoplasms at multiple sites and at all concentrations. IARC also evaluated the published HLE (1981) long-term study showing tumors developing at multiple sites in male and female Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene (Owen et al., 1987) and a comparative study in B6C3F$_1$ and NIH Swiss mice examining the role of endogenous retroviruses on the induction of lymphomas by 1,3-butadiene (Irons et al., 1987). IARC also presented some evidence showing that the metabolites 1,3-epoxybutene and 1,2:3,4-diepoxybutane possessed carcinogenic activity.

Epidemiologic studies evaluated by IARC (1992) consisted primarily of the studies published since 1982. The following studies were evaluated: (1) the mortality study conducted by Meinhardt et al. (1982) of workers in two styrene-butadiene rubber plants, but not the most recent update of this study by Lemen et al. (1990); (2) the mortality study by Downs et al. (1987)

of workers who manufactured 1,3-butadiene monomer and the most recent update of this study by Divine (1990); (3) a mortality study by Matanoski et al. (1989) of workers in eight U.S. and Canadian styrene-butadiene rubber plants (update of the study by Matanoski and Schwartz, 1987); (4) a nested case-control study of the 59 workers from the eight U.S. and Canadian plants who died from lymphopoietic cancer (Santos-Burgoa, 1988; Matanoski et al., 1990); (5) a nested case-control study of rubber workers dying from various types of cancer including lymphohematopoietic cancer (McMichael et al., 1976); and (6) a population-based case-control study of various types of cancers (excluding leukemia) conducted in Montreal, Canada (Siemiatycki, 1991).

Supporting evidence evaluated by IARC (1992) included in vitro studies on the metabolism of 1,3-butadiene using human liver and lung homogenates and comparative in vivo and in vitro metabolism studies in mice, rats, and monkeys. A detailed discussion on in vivo and in vitro genetic toxicity of 1,3-butadiene and metabolites (1,2-epoxybutene and 1,2:3,4-diepoxybutane) was presented along with other available information on short-term toxicity and nonneoplastic effects of 1,3-butadiene in humans and experimental animals.

IARC (1992) concluded that the evidence for the carcinogenicity of 1,3-butadiene in humans is "limited" based on (1) a study showing an increased risk for lymphosarcoma and reticulosarcoma among workers who manufacture 1,3-butadiene monomers; (2) a suggested increased risk for leukemia among workers at one of two styrene-butadiene rubber plants studied; (3) no increase of leukemia among the entire cohort of workers at eight U.S. and Canadian styrene-butadiene rubber plants, but a significant risk of leukemia among a subgroup of production workers; and (4) a large excess of lymphohematopoietic cancer nested among workers exposed to 1,3-butadiene in styrene-butadiene rubber plants. IARC also concluded that the evidence for the carcinogenicity of 1,3-butadiene in experimental animals was "sufficient" based on tumor induction at multiple sites in mice and rats, the induction of neoplasms in mice at all concentrations tested (6.25 to 1,250 ppm), the carcinogenicity of two metabolites of 1,3-butadiene, and the detection of activated K-*ras* oncogenes in lymphomas, liver tumors, and lung tumors induced by 1,3-butadiene. Evidence from metabolism and genetic toxicity studies supported the conclusions of the carcinogenicity studies. IARC (1992) concluded that 1,3-butadiene is *probably carcinogenic to humans* (Group 2A).

1.2.3. Summary of the National Institute for Occupational Safety and Health (NIOSH) Evaluation of 1,3-Butadiene (NIOSH, 1991a)

NIOSH (1991a) conducted a qualitative and quantitative assessment of the carcinogenicity of 1,3-butadiene. The evaluation of animal data focused on the studies that could be used for quantitative assessment, namely the studies using Sprague-Dawley rats (Owen et al., 1987) and

$B6C3F_1$ mice (NTP, 1984; Melnick et al., 1990a). The qualitative evaluation of the evidence from human studies focused on the studies by Downs et al. (1987) and updated by Divine (1990); Meinhardt et al. (1982) and updated by Lemen et al. (1990); Matanoski and Schwartz (1987) and updated by Matanoski et al. (1990); and a case-control study of the lymphopoietic cancers (Santos-Burgoa, 1988) from the Matanoski cohort. According to NIOSH, the results of this nested case-control study "provide the strongest human evidence to date for an association between 1,3-butadiene and the risk of lymphopoietic neoplasms, particularly leukemia." NIOSH concluded that overall the epidemiologic studies showed an increase in lymphopoietic neoplasms, which is consistent with the induction of lymphomas in mice exposed to 1,3-butadiene. However, NIOSH reported that the epidemiologic studies had certain limitations, such as the lack of historical exposure levels, the inclusion of both support and production personnel whose exposure would probably be minimal, and the inconsistent diagnosis of the different types of lymphohematopoietic neoplasms.

NIOSH reported on metabolism, pharmacokinetics, and disposition studies; their evaluation focused primarily on studies that provided data for estimating metabolic rates at low concentrations and comparison of metabolic pathways and rates in different species (mice, rats, monkeys, and humans). With respect to genetic toxicity, NIOSH did not focus on details of any studies, but noted that 1,3-butadiene is mutagenic in *Salmonella* with metabolic activation, whereas the metabolites are mutagenic without metabolic activation.

NIOSH (1991a) concluded that the present evaluation supports the conclusion of a previous evaluation (NIOSH, 1984), which stated that "1,3-butadiene should be considered to represent a potential human health hazard with respect to carcinogenicity." The basis for the conclusion was positive evidence of carcinogenicity in three long-term animal bioassays in two species, positive evidence of mutagenicity and genotoxicity, and less conclusive epidemiologic evidence of excess deaths from lymphopoietic neoplasms.

NIOSH used data from the study in $B6C3F_1$ mice (Melnick et al., 1990a) for its quantitative assessment because the lowest concentration (6.25 ppm) was similar to the proposed OSHA standard of 2 ppm. Weibull's one-, two-, and three-stage time-to-tumor models were used to derive the maximum likelihood and 95% confidence limit estimates on excess risk. The models were fit for the individual tumors for which the incidences were significantly higher in exposed groups than in control groups of male and female mice. Hemangiosarcomas of the heart and lymphomas were modeled as fatal lesions and all others as incidental lesions. The equivalent human doses were calculated based on body weight to the three-fourths power ($BW^{3/4}$) and converted back to ppm exposures in the workplace for 45 years of exposure. The excess risk for lifetime occupational exposure at 1 ppm was 305/10,000 based on lung neoplasms in females (highest) and 0.03/10,000 based on heart hemangiosarcomas in females.

NIOSH (1991b) discussed the uncertainties associated with its assessment. The dose-scaling method chosen and species differences in the metabolism of 1,3-butadiene were major sources of uncertainty. Another source of uncertainty was the most relevant tumor site used to predict human risk. The female lung was the most sensitive site, but based on the epidemiologic evidence, lymphomas may be the most relevant neoplasms. Other sources of uncertainty were the model selection: (1) whether the Weibull time-to-tumor model was the most appropriate and which stage model to use, (2) the assumption regarding lethality of tumors and omission of the high-dose group, and (3) estimation of the internal dose and the application of kinetic data.

1.2.4. California Air Resources Board (CARB, 1991)

The CARB (1991) evaluated the data on 1,3-butadiene and presented quantitative estimates of the cancer risk from inhalation exposure to 1,3-butadiene in ambient air. The literature review consisted of toxicokinetic data that focused on information presented by Bond et al. (1986, 1987) for absorption and tissue distribution data and reports published between 1985 and 1991 for metabolism and excretion data. Acute, subchronic, and noncancer chronic toxicity information was obtained from excerpts from EPA's 1985 carcinogen assessment document, and reproductive/developmental toxicity data and genetic toxicity data were reported from the primary literature. Genetic toxicity data focused on mutation tests in *S. typhimurium*, DNA alkylation studies, SCE and chromosome aberration tests, and various in vivo studies.

Animal carcinogenicity studies evaluated by CARB included the two NTP studies in mice (NTP, 1984; Huff et al., 1985; Melnick et al., 1990a), the inhalation study in rats (Owen et al., 1987), the role of retroviruses in 1,3-butadiene-induced carcinogenesis (Irons et al., 1987), and the expression of oncogenes in tumors induced by 1,3-butadiene (Goodrow et al., 1990). Human studies evaluated by CARB started with the 1976 study by McMichael et al. and continued through the 1990 reports by Lemen et al., Divine, and Matanoski et al. CARB discussed several factors that must be considered when interpreting the epidemiologic studies: (1) misclassification of exposure—unexposed individuals classified as exposed would bias the results toward the null; (2) exclusion of most highly exposed workers—studies in which the workers with the highest potential exposure (World War II workers) are excluded would be less likely to see a significant effect; (3) no dose-response effect—the lack of a positive association with duration of exposure should not discredit the study because the most recent NTP animal study (Melnick et al., 1990a) demonstrated that short-term exposure to a high concentration of 1,3-butadiene could be more effective than long-term exposure to low concentrations; and (4) varying health endpoints—there were inconsistencies in the subtypes of lymphopoietic and hematopoietic cancers observed in the various studies, but nomenclature changed over time and there are probably close relationships between the different subtypes. CARB presented four points of evidence for an association

between exposure to 1,3-butadiene and lymphopoietic and hematopoietic cancers in humans. The first point is that the strongest effect was observed in the cohort involved in the production of 1,3-butadiene monomer, and this cohort had the greatest potential for exposure to 1,3-butadiene in the absence of styrene. The second is that the observations of cancers in cohorts having potential exposure to styrene and 1,3-butadiene are consistent with the findings from the cohort from the 1,3-butadiene monomer production facility. The third point is presented in the case-control study by Matanoski and Schwartz (1987) and the cellular study by Checkoway and Williams (1982) in which both attributed the observed effects to 1,3-butadiene exposure and not to styrene exposure. The fourth point is that the cancers observed in humans are consistent with those observed in the mouse experiments. CARB concluded that "the epidemiological studies reported to date give evidence for increased incidences of leukemia and/or lymphohematopoietic neoplasms resulting from exposure to vapors in styrene-butadiene rubber plants or butadiene production plants." They further stated that the evidence for elevated rates of stomach and lung cancers is inconclusive.

CARB conducted an extensive quantitative assessment of the risk from exposure to 1,3-butadiene. The two mouse studies and the rat study were considered suitable for quantitative evaluation. Dose estimations were based on experimental (applied) dose, continuous internal dose, metabolized dose, target tissue dose, and molecular tissue dose. CARB used the retention data from Bond et al. (1986) to estimate the daily dose adjusted for 7-day week exposures (internal dose). The pharmacokinetics model of Hattis and Wasson (1987) was used to estimate internal exposure to metabolites, namely butadiene monoepoxide (metabolized dose). The tissue distribution data of Bond et al. (1986, 1987) were used to estimate the target tissue doses, which were not used for risk estimation because the data were not reliable. Sufficient data on DNA adducts were not available for deriving molecular tissue doses.

CARB fitted the experimental (applied dose), internal, and metabolized doses estimated from the first mouse study (NTP, 1984) to the linearized multistage (Global 86) and the Weibull time-to-tumor models; the cancer potency estimates derived using the linearized multistage model and Weibull's model gave similar results. The multistage model was used to derive cancer potency values using the second mouse study (Melnick et al., 1990a) and the rat study (HLE, 1981). Cancer potency estimates were derived for each anatomical site separately and for the total number of tumor-bearing animals with significantly increased tumors in both males and females. The human cancer potency estimates, based on 70 years of continuous exposures, derived from the first mouse study using the total significant tumors, the internal dose, and the multistage model were 0.32 $(ppm)^{-1}$ or 0.59 $(mg/kg/day)^{-1}$ for male mice and 0.18 $(ppm)^{-1}$ or 0.33 $(mg/kg/day)^{-1}$ for female mice. Cancer potencies derived from applied doses were about 10-fold lower, and those derived from metabolized doses were about 50% lower. The human cancer

potency estimates using the rat data (total significant tumors), internal dose, and the multistage model were 1.8×10^{-3} $(ppm)^{-1}$ or 8.4×10^{-3} $(mg/kg/day)^{-1}$ for male rats and 3.5×10^{-3} $(ppm)^{-1}$ or 1.6×10^{-2} $(mg/kg/day)^{-1}$ for female rats. The estimates based on applied or metabolized doses were much lower. The data from the second mouse study were analyzed extensively; CARB concluded that the best human cancer potency estimates based on internal doses and estimated using the multistage model (Global 86) were 0.37 $(ppm)^{-1}$ or 3.4 $(mg/kg/day)^{-1}$ derived for alveolar/bronchiolar adenoma/carcinoma in female mice. The corresponding unit risk derived from the second mouse study was 1.6×10^{-4} $(\mu g/m^3)^{-1}$ and the exposure for the risk at 10^{-6} was 6.0×10^{-3} $\mu g/m^3$. From their cancer potency values, CARB estimated the lifetime extra risk associated with exposure to 1 ppb 1,3-butadiene to range from 9.8×10^{-6} to 3.7×10^{-4}, which corresponds to 10 to 370 additional cases per 1 million individuals.

1.2.5. Summary of Findings by U.S. Occupational Safety and Health Administration (OSHA)

The most recent analysis of health effects of 1,3-butadiene by a government entity is by OSHA (1996). While the analysis in general is similar to that of NIOSH, OSHA incorporated a recent update of the large SBR polymer retrospective follow-up study that had been started by Matanowski et al. This update, Delzell et al (1995), included not only an additional period of follow-up, but also a detailed exposure history for 1,3-butadiene, styrene, and benzene for more than 15,000 employees who had worked in SBR and related activities at the eight study plants. Delzell et al. concluded that "This study found a positive association between employment in the SBR industry and leukemia. The internal consistency and precision of the results indicate that the association is due to occupational exposure. The most likely causal agent is BD or a combination of BD and [styrene]. Exposure to [benzene] did not explain the leukemia excess." OSHA in its analysis of the Delzell et al. and previous studies recognized these consistencies and similarly concluded that "there is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system. The epidemiologic findings supplement the findings from the animal studies that demonstrate a dose response for multiple tumors and particularly for lymphomas in mice exposed to BD" (OSHA, 1996, p. 56764).

OSHA also examined the evidence for reproductive and developmental effects. Analyzing data from both the NTP I and the NTP II studies, OSHA noted the consistency and dose response and concluded "that exposure to relatively low levels of BD resulted in the induction of ovarian atrophy in mice..." (OSHA, 1996, p. 56765). For the total database on these and mutagenic effects, OSHA concluded that "these animal studies taken as a whole, offer persuasive qualitative evidence that BD exposure can adversely affect reproduction in both male and female rodents. The Agency also notes that BD is "mutagenic in both somatic and germ cells" (p. 56767).

For quantitative risk assessment, OSHA's analysis was very similar to that of NIOSH (1991a) in its choice of data set (NTP II mouse study), model (multistage Weibull), treatment of tumors (dose-response analysis on an individual basis), treatment of fatal vs. nonfatal in the time-to-tumor analysis, choice of parsimonious model algorithm (fewest parameters of the multistage model that provide an adequate fit to the data) and reporting of the ML estimates. The major difference between the NIOSH and OSHA analyses was that OSHA used (mg/kg bw-day) equivalence for species conversion instead of the $BW^{3/4}$ conversion used by NIOSH. This change of species conversion factors and some minor modifications relating to animal weights and breathing rates decreased OSHA's potency estimates by a factor of approximately 4 from the NIOSH estimates. Based on the female mouse lung tumor response, the OSHA ML estimate of potency was 8.1×10^{-3} $(ppm)^{-1}$ for an occupational lifetime of exposure to 1 ppm, 5 days/week, 50 weeks/year for 45 years. If this potency estimate is extrapolated to be based on a 70-year continuous lifetime exposure, the OSHA estimate would be approximately 36.7×10^{-3} $(ppm)^{-1}$. Based on the OSHA risk assessment, their permissible exposure limit was lowered from 1,000 ppm to 1 ppm with a 15-min short-term exposure limit.

1.3. DISCUSSION

Six different carcinogenicity assessments of 1,3-butadiene, done by five different agencies in different time periods, are summarized in this chapter. The major conclusions of these evaluations are presented in Table 1-1.

Although no apparent agreement is evident from the table among the five agencies' assessments, in fact they are very similar. Both EPA (1985) and IARC (1986) conclude that the carcinogenicity evidence in humans is inadequate and in animals is sufficient. But due to different classification systems, they get different alphabetical assignments, i.e., B2 and 2B, which correspond to "probable" and "possible" descriptors, thus appearing to be in disagreement with each other. NIOSH and OSHA both use the dichotomous descriptors with "potential occupational carcinogen" being the highest ranking.

Table 1-1. Carcinogenicity assessments of 1,3-butadiene

Agency (year)	Cancer classification	Quantitative risk	Remarks
EPA (1985)	"B2-probable human carcinogen" —based on inadequate human and sufficient animal evidence.	Unit risk to humans—2.5 × 10^{-1} $(ppm)^{-1}$ based on NTP (1984) mouse data.	Cancer classification using EPA carcinogen assessment guidelines.
IARC (1986)	"2B-possible human carcinogen"—based on inadequate human and sufficient animal evidence.	No quantitative risk presented.	Cancer classification using IARC system.
IARC (1992)	"2A-probable human carcinogen"—based on limited human and sufficient animal evidence.	No quantitative risk presented.	
NIOSH (1991a)	"Potential human health hazard with respect to carcinogenicity."	Range of excess risk at 1 ppm is MLE of 305/10,000 based on female mouse lung neoplasms to MLE of 0.03/10,000 based on heart hemangiosarcomas in females. Data from Melnick et al. (1990a) used for this quantitation.	OSHA cancer policy classification system used. Quantitative risk is for occupationally exposed populations.
CARB (1991)	No formal classification given	Human cancer potency based on mouse data from Melnick et al. (1990a) range for 1 ppb exposure—9.8×10^{-6} to 3.7×10^{-4}.	No formal cancer classification system used. Quantitative risk is for general population.
OSHA (1996)	Potential occupational carcinogen	Human cancer potency estimate based on female mouse lung neoplasms. MLE is 8.1×10^{-3} $(ppm)^{-1}$.	"Convincing evidence that BD is a probable human carcinogen." Quantitative risk is for occupationally exposed populations.

OSHA, NIOSH, and CARB assessments all state that the human evidence is strongest for an association between butadiene exposure and the occurrence of lymphohematopoietic cancers. The same evidence is described as "limited" human evidence by IARC, which elevates the classification of this compound to "2A-probable human carcinogen." Furthermore, it should be noted that the quantitative risk estimates appear to be different for OSHA/NIOSH and EPA/CARB. NIOSH/OSHA quantitative risk estimates are for occupationally exposed populations, while quantitative estimates of CARB are for general population (lifetime risk), even though they are derived from the same animal data.

The apparent differences in these assessments thus can be explained by availability of the studies at the time of evaluations, different cancer classification systems, and quantitative assessments done for different purposes.